Comments of Dr. Geoffrey Berry prepared for The Crystalline Silica Panel of the American Chemistry Council.

Comment 1. Introduction. This report has been prepared in response to a request from the American Chemistry Council's Crystalline Silica Panel dated 6 May 2003.

Response. *The American Chemistry Council's Crystalline Silica Panel submitted a separate set of public comments, which are responded to elsewhere. The comments of Dr. Berry and the Council overlap.*

Comment 2. Benchmark Approach**.**

2.1 The *Chronic Toxicity Summary* prepared by the California Office of Environmental Health Hazard Assessment (OEHHA') is concerned with the calculation of a Reference Exposure Level (REL) based on an estimate of an exposure level at which 1% of exposed people may develop silicosis. Such an estimation may be made from epidemiological data from studies in which the risk of silicosis has been determined in relation to exposure measures. The epidemiological studies used have been of occupationally exposed groups where the prevalence of silicosis has been higher than 1%. The exposure giving a risk of 1% may be estimated by fitting a model to the exposure-response relationship and, from the fitted values of the parameters of this model, finding the exposure corresponding to a 1% risk. This is the approach used for the key study in the *Chronic Toxicity Summary*.

2.2 Such an estimate has uncertainty, in the same way as anything estimated from an epidemiological study has uncertainty, due to random variability. Uncertainty of this kind is often expressed in terms of a confidence interval and in the benchmark approach the lower confidence limit is taken as the benchmark dose (BMD).

> *The BMD is defined as a sample statistic: 'a statistical lower confidence limit on the dose producing the predetermined level of change'. ..... An example of a BMD is a 95% lower confidence limit for the dose producing a 1% increase in adverse response compared with the unexposed (untreated) case.*
>
> (Barnett & O'Hagan, 1997, page 72)

The approach in the example in the quotation above has been used in the *Chronic Toxicity Summary* with the assumption that the unexposed case produces no silicosis (by definition this is clearly a correct assumption, but depends on silicosis being unambiguously determined).

Response. *OEHHA staff concurs with the above comment.*

Comment 3. Key study

3.1 The key study is that of Hnizdo & Sluis-Cremer (1993).

3.2 Hnizdo and Sluis-Cremer (1993) considered the onset of silicosis during follow-up to the end of 1991. Silicosis was defined as ILO category 1/1 of rounded opacities. Radiographs were read in chronological order for each miner independently by two readers, and the year of onset of silicosis was defined as the year when category 1/1 or higher was first read. The results of only

one of the readers was used, the one whose readings correlated most strongly with determinations at autopsy (Hnizdo *et al.*, 1993). The risk of silicosis was analysed in relation to dust exposure measured by duration and concentration of respirable dust (mg/m³). The cumulative risk of silicosis was assessed in terms of cumulative exposure using life table and survival analysis methodology. The cumulative risk was estimated as 25% for a cumulative exposure of 9 mg/m^3-years respirable dust and as 77% for a cumulative exposure of 15 mg/m^3-years of respirable dust with a stated average quartz content of 30%.

3.3 The key data summary was set out in Table IV of Hnizdo and Sluis-Cremer (1993) as follows:

Midpoint CDE[1] (mg/m³-yr)	No. cases	No. at risk
1	0	2218
3	9	2014
5	48	1540
7	85	984
9	93	515
11	53	197
13	20	55
15	5	11

[1] CDE is the cumulative dust exposure; the authors noted that 30% of this was quartz

3.4 This table was headed "Life Table Results for the Risk of Silicosis ...." Referring to the Methods section of the paper (sub-section Determination of Silicosis Onset) we have:

> *The miners had an annual radiological examination while working in the mines, and subsequently most of the miners came for an occasional radiological examination.* (page 448)
>
> *The radiographs of each miner were read blindly, in a chronological order starting from the most recent radiograph, by two independent readers. The onset of silicosis was defined as the year when rounded opacities of ILO category 1/1 or higher were first read.* (page 449)

It is on that basis that the data are set out in a life table format. In the *Chronic Toxicity Summary* (page 21) it is stated that

> *This study was powerful enough to detect a 1.9% incidence of silicosis (9 cases out of 474 exposed) at 0.9 mg/m³-yr silica.*

These figures have apparently been taken from the above table as follows:

> CDE =3 mg/m³-yr multiplied by 30% giving 0.9 mg/m³-yr silica; 9 cases in this subgroup, number at risk = 2014 – 1540 = 474. 9 cases in 474 equals 1.9% incidence.

I believe this to be an incorrect interpretation of the results presented in the paper. There were 9 men, whose exposure at their earliest radiograph indicated silicosis, in this exposure category. There were 465 men, whose exposure at their most recent chest radiograph (did not indicate silicosis), in this exposure category. This gives a total of 474 men. But there were 1540 men whose exposure was higher. For these 1540, it is known that when they were in the lower exposure categories, they did *not* have silicosis (this is known because there were annual radiographs throughout exposure, and the earlier radiographs did not show silicosis). Consequently the 9 cases go with a denominator of 2014, as was used by Hnizdo and Sluis-Cremer (1993), rather than with a denominator of 474. This gives an incidence of 0.4%, which is consistent with Hnizdo and Sluis-Cremer's interpretation of the data. (It is clear from Figures 1 and 2 of Hnizdo and Sluis-Cremer that the risk at a CDE of 3 mg/m³-yr is much less than 1.9%.)

On page 7 of the *Chronic Toxicity Summary* the value '474' and corresponding numbers for the other exposure categories are described as 'the total number of miners actually at each (midpoint) level'. Repeating the point made in the previous paragraph, this ignores the fact that there were another 1540 men who had been at that level and whose chest radiograph, when they were at that level, was negative.

It has to be noted that, whilst 1.9% is certainly an overestimate of the silicosis incidence rate for workers in the 3 mg/m³-yr exposure category, 0.4% may be an underestimate since, as noted by Hnizdo and Sluis-Cremer, the association is confounded by latency. That is, it is possible that had some of the 1540 men who went on to higher exposures before developing silicosis left the mines whilst still in the 3 mg/m³-yr exposure category, they may have still developed silicosis in the absence of further exposure. Hnizdo and Sluis-Cremer noted that for 135 miners, the onset of silicosis occurred while the miners were still working at the mines, and for the other 178, onset was an average of 7.4 years (range 0.1 to 25) after leaving the mine.

3.5 The data to which the benchmark concentration methodology was applied in the *Chronic Toxicity Summary* were:

Exposure (mg/m³-yr)	No. cases	No. of subjects in group
1	0	204
3	9	474
5	48	556
7	85	469
9	93	318
11	53	142
13	20	44
15	5	11

I ran BMDS Version 1.3.1 (downloaded from the Internet) with the above data format—that is, I used OEHHA's assumption that the number at risk in the 3 mg/m³-yr exposure category was only 474, etc. In agreement with OEHHA, I found a BMC (1% risk, lower 95% limit) of 2.12 mg/m³-yr cumulative dust exposure, and a BMC (5% risk, lower 95% limit) of 3.73 mg/m³-yr (and I also agreed with the goodness-of-fit statistics given by OEHHA). Since these estimates were obtained using an incorrect interpretation of the data (with denominators that are too low) as discussed in §3.4, the risks are too high, and consequently the benchmark concentration estimate is too low.

3.6 I then ran the BMDS program using the data as set out in §3.3 - that is, on the assumption that the number at risk in the 3 mg/m³-yr exposure category was 2014, etc. This gave a BMC (1% risk, lower 95% limit) of 3.46 mg/m³-yr cumulative dust exposure, and a BMC (5% risk, lower 95% limit) of 5.52 mg/m³-yr. These estimates are in accord with Figure 2 of Hnizdo and Sluis-Cremer but, for the reasons discussed in §3.4, may be too high. (Also this run did not take the life table nature of the data into account, as I could not see how to do this within BMDS, but this is not too much of a problem when using the fitted relationship at the lower exposure end of the relationship).

3.7 To summarize the above, it seems that the estimate of a BMC (1% risk, lower 95% limit) of 2.12 mg/m³-yr is too low, and that 3.46 mg/m³-yr is likely to be a more accurate estimate. Assuming the data reported in Hnizdo and Sluis-Cremer are correct, the correct figure is somewhere between these values. I doubt it is possible to determine exactly where in between these values the correct figure lies; but in the next section I explore some scenarios.

3.8 In an attempt to narrow down the range of 2.12 to 3.46 mg/m³-yr, I have proceeded as follows. First, the fitted exposure value for a 1% response is determined mainly by the data at the lower exposure levels of the exposure-response relationship. Second, to fit the exposure-response relationship, two exposure categories with a non-zero number of cases are required. Thus, for the tabulation in §3.3 the first three rows of data are needed.

If the BMDS program is run using just these three rows of data, then the BMC (1% risk, lower 95% limit) is estimated as 3.33 mg/m³-yr. The similarity of this value with the estimate of 3.46 mg/m³-yr obtained using the full data (§3.6) confirms that the estimate is determined mainly by the lower exposure levels.

Next, arguing along the lines discussed in §3.4 that some of the men who did not develop silicosis whilst in the 3 and 5 mg/m³-yr cumulative exposure categories, may have developed silicosis later in life, even if they had ceased exposure whilst still in the 3 and 5 mg/m³-yr cumulative exposure categories, I have repeated the BMDS calculations assuming a doubling and a tripling of the numbers of cases in these two categories. The results are summarized as follows:

Midpoint CDE[1] (mg/m³-yr)	No. at risk	Observed no. of cases	Double no. of cases	Triple no. of cases
1	2218	0	0	0
3	2014	9	18	27
5	1540	48	96	144
BMC (1%)		3.33	2.82	2.59

3.9 From the Hnizdo and Sluis-Cremer paper, there seems little to justify taking the risk in the lower exposure groups, after allowing for latency, as more than double the observed risks of 0.4% and 3.1%. Accordingly, I will take the value of 2.8 mg/m³-yr, corresponding to a doubling of the observed number of cases, as a lower bound to the BMC, and will use that value in addition to the value of 3.46.

3.10 As noted in the *Chronic Toxicity Summary* (page 22) a benchmark analysis was carried out by USEPA in 1996 (EPA 1996, chapter 7 pages 7-4 to 7-5) using the data of Hnizdo and Sluis-Cremer (1993). In the EPA Report the exposures were converted to silica prior to fitting the model, and the lower bound for a 1% risk was estimated as 1.31 mg/m³-yr cumulative *silica* exposure. To make this value comparable with the values discussed above, it has to be converted back to cumulative dust exposure and, with 30% of the dust being silica, the value is equivalent to 4.37 mg/m³-yr cumulative dust exposure, which is higher than any of the values discussed above. In the EPA report the exposure-response model used was the log-logistic model, as also used by Hnizdo and Sluis-Cremer, whilst in the *Chronic Toxicity Summary* a log-dose probit model was used.

Response. *OEHHA staff appreciates the thorough review and the reproduction of our calculations by the commentator. However, contrary to the suggestion in this comment, the 1.9% incidence (9 cases/474 exposed) is the correct value for use in the benchmark concentration. The benchmark dose method is not a pair-wise group-to-group comparison, but involves a fit to the entire data set. All non-responding individuals are considered in the fit regardless of the exposure group to which they are assigned. This point is discussed at length in OEHHA's responses to comments of the American Chemistry Council. The approach to determining the population at risk described in the comment appears to derive from that given in the original publication as part of a life table analysis. Life tables were developed to analyze survival. They can be used (1) to ask the question whether silica-exposed workers live as long as unexposed workers and (2) to identify, in conjunction with other tests such as chest radiographs, when they get silicosis. Although the life-table methodology is validated as a tool for description of the health outcomes within a measured cohort, it is seldom used to predict health protective levels in groups other than that represented in the population studied. It has also been used as a tool in examining the relationship between risk and the intensity and duration of exposure in cases where there is an expected continuous relationship between population risk and cumulative exposure, such as the examination of increments in relative cancer risk (for tumors with a background incidence in the population) with duration of exposure. OEHHA has chosen to apply an entirely different type of analysis, i.e. the benchmark dose methodology, for estimating a health protective dose level. This makes no attempt to predict future outcomes in the exposed groups; it is not a time-dependent analysis in that sense. The desired objective is the identification of a health protective level at which no cases of the critical end-point (silicosis) would be observed at any time, not the estimation of a time- and dose-related incidence rate. It should be noted that all members of the study population, whether affected by silicosis or not, are considered by the benchmark dose methodology: this is a model fit to the entire population, not a comparison between groups.*

Comment 4. Exposure data

4.1 The benchmark concentration calculations are, of course, dependent on the accuracy of the exposure estimates. As noted by Gibbs and Du Toit (2002)

> *for several years there has been some suspicion that silicosis risks in South African studies were over-estimated because of underestimates of dust and silica exposure.*
>
> *They (that is, Hughes and Weill, 1995 and Muir et al. 1989) suggested that South African exposures were underestimated, a possibility acknowledged by the original author.*

4.2 Gibbs and Du Toit carried out a thorough assessment of the methods that had been used in the South African studies to estimate exposure, working from original documentation in South Africa. They concluded

> *the quartz exposures of South African miners derived from past theoretically based conversions from particle number to respirable mass underestimate the actual quartz exposures by a factor of about 2.*

This means that the figures given earlier should be multiplied by 2, so that the values of 2.8 and 3.46 mg/m³-yr discussed in §3.9 become 5.6 and 6.9 mg/m³-yr, respectively.

Response. *OEHHA staff has reviewed the Gibbs and Du Toit (2002) paper for possible application to the cREL derivation. OEHHA's responses to comments by the American Chemistry Council and to comments by Dr. Gibbs address this in detail. In summary, acceptance of the Gibbs and Du Toit analysis would change the percent quartz in the South African gold mine dust from 30% to 54%. However, Gibbs and Du Toit (2002) cite the work of Kielblock and coworkers (1997) indicating that recent measurements of mine dust indicate 15% respirable quartz content. Dr. Eva Hnizdo cites other available studies showing approximately 20% quartz in the mine dust. Thus OEHHA staff is reluctant to accept only the highest value available (54%) for % quartz in the mine dust. Rather, we have chosen the value reported in the study, which falls approximately mid-range of other estimates.*

Comment 5. Supporting Study (1)

5.1 The first supporting study used in the *Chronic Toxicity Summary* was that of workers at the Homestake goldmine in South Dakota reported by Steenland and Brown (1995). In this study, silicosis was identified either from death certificates or from x-rays taken at two cross-sectional surveys; 75% were identified by death certificate only.

5.2 The authors note that some of the 5 cases of silicosis with a low cumulative exposure, < 0.2 mg/m^3 – years, may have been due to silica exposure "before or after working at the gold mine" (page 1375, col 2). They also note that some deaths due to chronic obstructive pulmonary disease may have been "misdiagnosed as silicosis" (page 1373, col 3).

5.3 It should also be noted that in this paper, the examination of lifetime risks using a life table is an invalid approach, as the observations in Steenland and Brown are of prevalence, not of incidence, and the dates of incidence are unknown. This refers to Table 3 of Steenland and Brown, which was reproduced as Table 8 in the *Chronic Toxicity Summary* (page 10). This

means that the risk figures given in the paper are overestimates of the actual risk because of the use of prevalence rates as if they were incidence rates. Thus, for example, there were 52 miners with an exposure exceeding 4 mg/m^3-years, and 26 of these had silicosis by the above definition. The cumulative risk for miners with at least 4 mg/m^3-years of exposure is thus 50%, not 84% as calculated by the lifetime method.

5.4 I have reproduced the BMDS analysis quoted in the *Chronic Toxicity Summary,* agreeing with the BMC estimate of 0.43 mg/m^3-yr, and noting that the model did not fit well. I note that the numbers at risk that were used are the numbers in parentheses in the third column of Table 8 in the *Chronic Toxicity Summary* (page 10). The use of these figures is correct since so doing corrects for the invalid approach given in the paper (§5.3). (This is the opposite position to my criticism of the approach in the *Chronic Toxicity Summary* to the Hnizdo and Sluis-Cremer data. In that case the authors' life table approach is valid whereas here the authors' presentation is invalid).

5.5 The problems arising out of diagnosing silicosis mainly from death certificates with the possibility of a certification bias because of known occupational history, past worker's compensation claims etc. mean that this study is not strong in terms of defining an exposure-response relationship. Further complicating the derivation of an exposure-response relationship in this study is the uncertainty surrounding the estimates of exposure. For example, there were no dust measurements for the period prior to 1937, even though 92% of the cases had 50% of their work history during that period.

Response. *OEHHA staff agrees that the Steenland and Brown paper has some shortcomings. OEHHA has obtained better fits of the BMD models to the Steenland and Brown data by dropping high exposure levels. Fitting the probit model to the log dose of the five lowest silica levels from Steenland and Brown yielded a BMC_{01} of 0.34 (mg/m^3)–yr CDE (χ^2 = 1.32; p value for fit = 0.5177). Use of the BMC value from the probit model resulted in a chronic REL estimate of 4 μg/m^3. Despite the methodological difficulties, we think that it is appropriate to estimate a chronic REL from this study for comparison to those derived from other studies. As noted, we did not use this study to derive the proposed chronic REL for crystalline silica.*

Comment 6. Supporting Study (2)

6.1 The second supporting study used by OEHHA was that of workers in the diatomaceous earth industry reported by Hughes *et al.* (1998).

6.2 In the *Chronic Toxicity Summary*, emphasis is placed on the 6 cases that occurred with a cumulative exposure of less than 1 mg/m^3-yr. These cases are defined in terms of chest X-ray readings as small opacities of profusion of 1/0 or greater, *considering both rounded and irregular opacities*. Out of 81 positive, there were only 37 with a profusion of 1/1 or greater of predominantly rounded opacities. This should be borne in mind when comparing the results with those from the South African study – the definition used by Hughes *et al.* for silicosis is less strict than that in the South African study.

6.3 The inclusion of both rounded and irregular opacities, and of opacities of profusion 1/0, raises the question of the positive predictive value of this grouping as a definition of silicosis. The authors discussed this point, noting small opacities have been observed in unexposed groups

and that a meta-analysis had reported a prevalence of 1.3% for small opacities of 0/1 or greater in North American men (page 813, col 1).

6.4 The *Chronic Toxicity Summary* tends to be dismissive of the issue discussed in §6.3, arguing that "due to the rarity of silicosis" the six cases in the lowest exposure grouping are "biologically significant" and that "OEHHA considers that the six cases may be work related, not cases of environmental or background silicosis". I think that this misses the point. Whilst silicosis is rare (or technically non-existent) in the unexposed, the question is whether category 1/0 including irregular opacities is unambiguously silicosis. From the evidence cited by Hughes *et al.*, it is apparent that category 1/0 is not necessarily the same as silicosis. Thus, it is not so much a question of whether the six cases had environmental or background silicosis, but rather whether they had silicosis at all. As noted in §2.2, the methodology used in the *Chronic Toxicity Summary* is dependent on the assumption that the unexposed group produces no cases. Of course, some of the six cases may be work related, but with a background rate of around 1%, there is no evidence from this study that the rate in the lowest exposure group is increased.

Response. *OEHHA staff would like to agree that it is "apparent that category 1/0 is not necessarily the same as silicosis." However, Hnizdo et al. (1993) found that among their South African gold miners with less than an ILO category 1/1 (i.e., 1/0, 0/1, and 0/0) nearly half showed varying (slight, moderate, or marked) levels of histological silicosis at autopsy.*

	Reader 1	*Reader 2*	*Reader 3*
ILO category < 1/1	*426*[a]	*475*[a]	*475*[a]
No silicosis at autopsy	*153*	*150*	*151*
Insignificant "	*75*	*73*	*75*
Slight "	*123*	*126*	*142*
Moderate "	*63*	*67*	*88*
Marked "	*12*	*12*	*19*
Marked + moderate	*75/426 = 17.6%*	*79/475 = 16.6%*	*107/475 = 22.5%*
Marked+mod+slight	*198/426 = 46%*	*205/475 = 43%*	*249/475 =52%*

[a] *Each reader read the same 557 radiographs. The remaining were classified as ≥ 1/1.*

From the point of view of protecting public health, staff would like to be assured that the opacities among the 6 diatomaceous workers at less than 1 mg/m³-yr exposure were unambiguously <u>not</u> silicotic. If there were rounded opacities present in any or all of the six people diagnosed by radiograph in the lowest silica exposure group, prudence indicates considering them to be silica related. Some observers also hold that the very beginnings of some silicotic nodules may be irregular opacities. Unfortunately it is not possible to distinguish such irregular small opacities postulated to be due to silica exposure from those due to smoking or aging.

Comment 7. <u>Summary.</u> Working from the *Chronic Toxicity Summary* the best evidence of an exposure-response relationship that may be used to calculate benchmark concentration values is the South African study. For the reasons given in sections 3 and 4, the BMC (1% risk, lower 95% limit) may be in the range of 5.6 to 6.9 mg/m³-yr, rather than 2.1 mg/m³-yr, for cumulative respirable dust exposure. After all the other adjustments for % silica composition, translation of

occupational exposure duration to an environmental exposure context, and the application of uncertainty factors, the estimated REL of 3 μg/m³ calculated in the *Chronic Toxicity Summary* would increase to the range of 8 μg/m³ to 10 μg/m³.

Response. *OEHHA staff appreciates the thoroughness of the comments. The largest source of the commentator's suggested increase in the cREL is the paper by Gibbs and DuToit (2002) indicating with much uncertainty that the % quartz in the mine dust was 54%, not 30%. Staff has reviewed the paper by Gibbs and du Toit (2002) and various other sources of pertinent data [particularly Kielblock et al. (1997)]. Although the points raised by Gibbs and du Toit (2002) may be valid in so far as they refer to that specific analysis of Hnizdo and Sluis-Cremer (1993), a consideration of the broader range of applicable data suggests that increasing the estimate of % quartz in the mine dust from 30% to 54% is not justified. The other source of change is the choice of the denominator of workers at risk for silicosis. That point as is applies to a benchmark dose analysis was addressed above. Thus staff believes that a cREL of 3 μg/m³ is appropriate.*

References (quoted by commentator)

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